



Armed Forces College of Medicine AFCM

Cardiopulmonary module





Treatment of Hyperlipidemia

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Pharmacology**

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INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

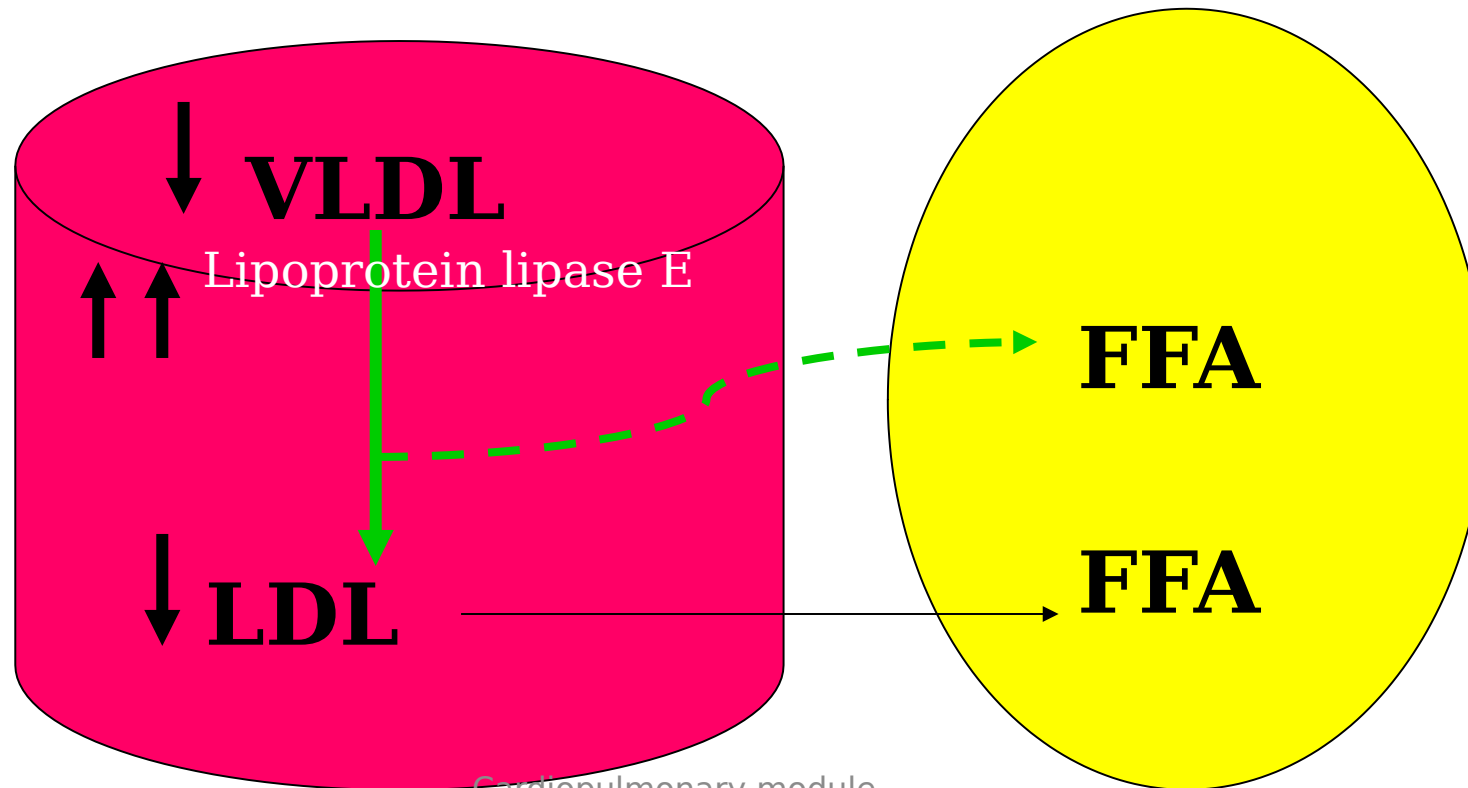
- 1-** Compare the mechanism of action and the adverse effects of the drug interaction of niacin, cholestyramine, cholesterol absorption inhibitors, and omega 3 fatty acids
- 2-** Relate the therapeutic uses of niacin, cholestyramine, cholesterol absorption inhibitors, and omega 3 fatty acids to their clinical applications
- 3-** List indications of combined therapy for hyperlipidemia treatment
- 4-** Explain favorable and unfavorable combinations
- 5-** Compare the mechanism of action of new antihyperlipidemic drugs.



III-Niacin (vitamin B3)



Niacin can reduce LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides



Mechanism of action:

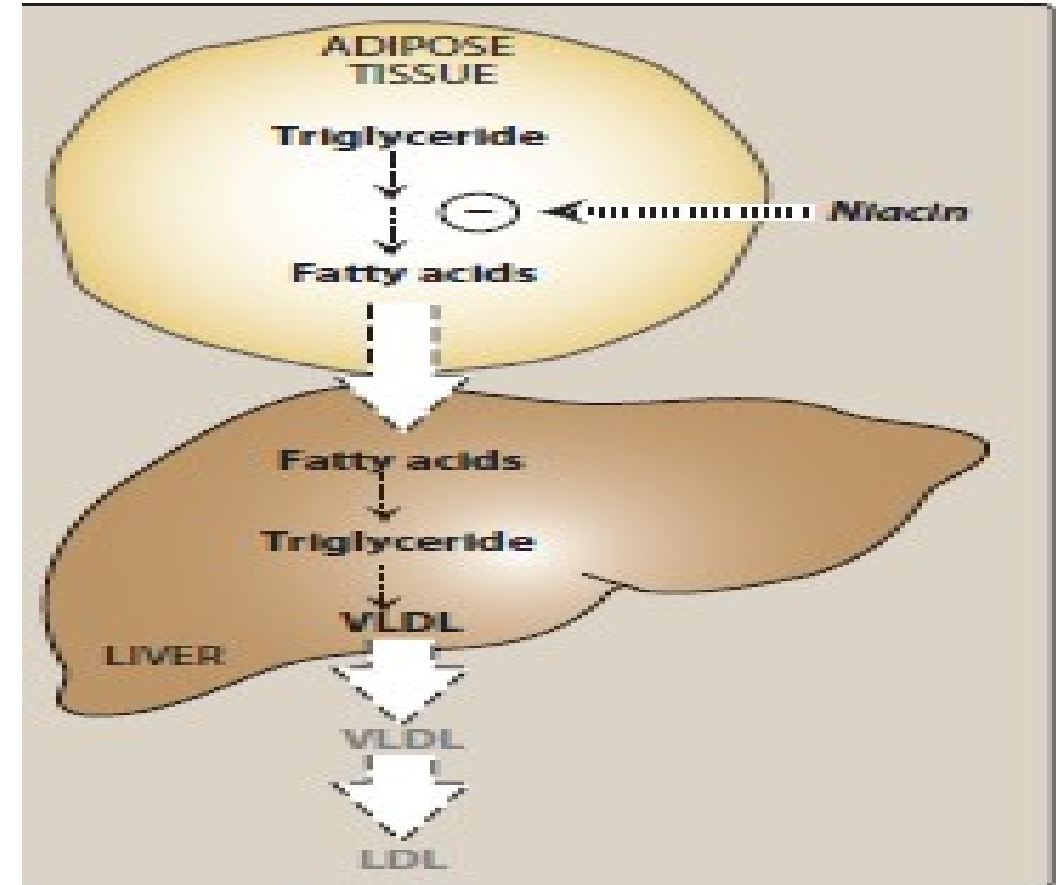


IN adipose tissue: Niacin binds to adipose nicotinic acid receptors; **inhibits lipolysis** this will lead to decrease in free fatty acids mobilization from adipocytes to the liver resulting in **decrease TG and thus VLDL synthesis**

(after few hours).

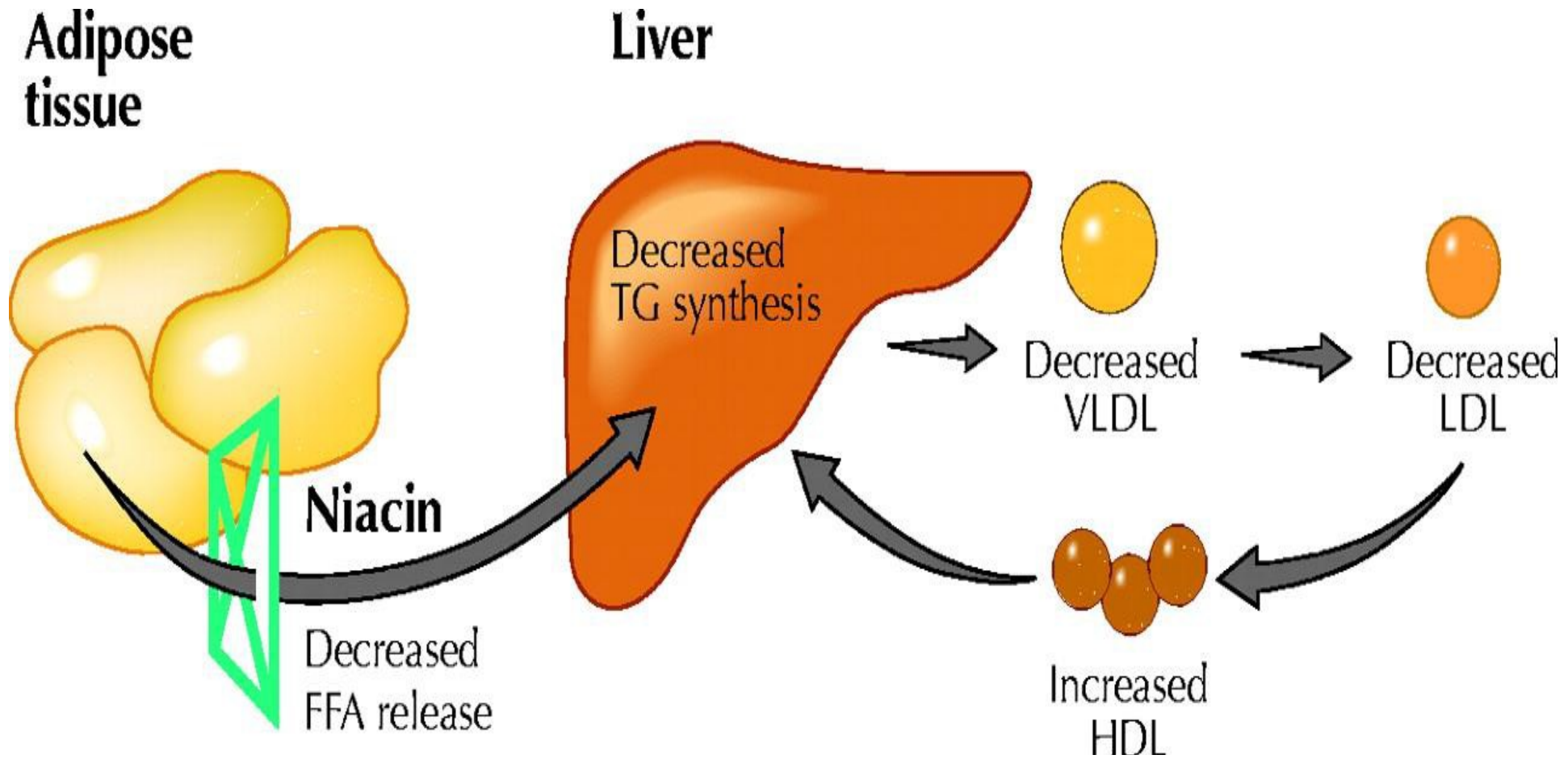
Since LDL is derived from VLDL, $\square$ VLDL
 $\square \square$ LDL (after few days)

Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma



Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer





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Uses:



e.g:

Nicotinic acid
(Vit B3)

not niacinamide
alone does not
decrease plasma
lipid levels

1. Mixed hyperlipidemia,
2. mixed with other drugs to treat hypercholesterolemia and hypertriglyceridemia



Side effects

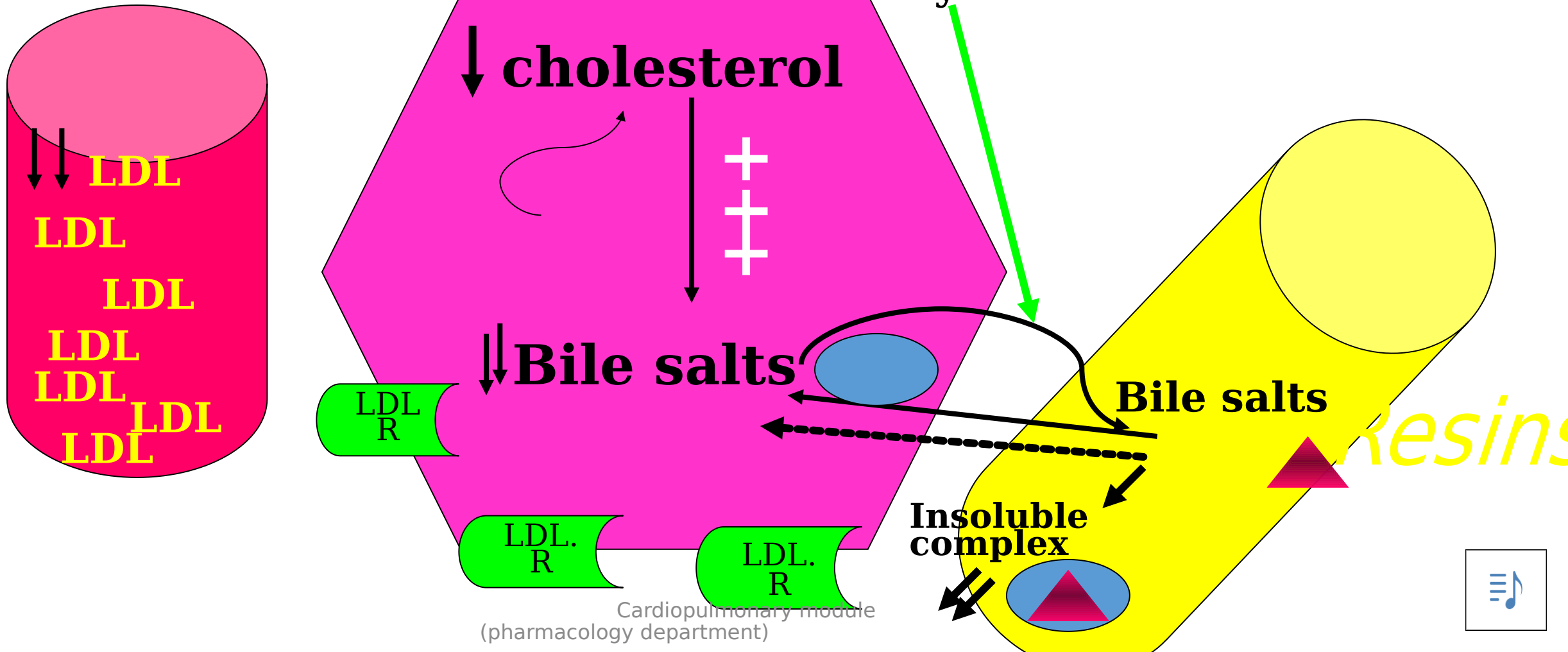


- a. **Cutaneous flush and pruritus (most common) due to local release of prostaglandins. *Avoided by aspirin.***
- b. **Gastric distress and nausea & abdominal pain. (it stimulates histamine release resulting in increased gastric motility and acid production)**
- c. **Gouty arthritis (decreased uric acid excretion)**
- d. **Glucose intolerance (an increase in insulin resistance so increase the dose of insulin or the oral agents).**
- e. **Reversible Elevated serum transaminase level (to twice normal may occur, usually not associated with liver toxicity).**



IV. Cholestyramine (Bile acid binding resins)

•Block enterohepatic cycle of bile salts



MECHANISM



- a. When resins are given orally, they are not absorbed.
- b. **Bind** to **bile acids** and **bile salts** in intestinal lumen, **prevent** their **reabsorption** and **increase** their excretion (10 fold), thus interrupt the enterohepatic circulation of bile acids forming complexes that are excreted in feces.
- c. The net effect, **causes the liver** to scavange more cholesterol from the body to make additional bile acids (which are essential components of the bile). Consequently, intracellular cholesterol concentrations decrease.
- d. This activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to **a fall** in plasma LDL-C (commonly known as "bad cholesterol").
- e. This increased uptake is mediated by an up-regulation of cell





Uses:

e.g:

Colestipol

Cholestyramine

Colesevelam

Should be taken with meals 3 times daily to be effective

hypercholesterolemia in patients who cannot tolerate other drugs, only for isolated increases in LDL.

2-Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis.

3-Effective in digitalis toxicity

Side effects

a. GIT upset (*Colesevelam* has fewer GI side effects than other bile acid sequestrants).

b. At high doses decrease absorption of fat soluble vitamins (A,



Interactions



1-Decrease Absorption of other drugs as warfarin, reductase inhibitors, thyroid hormone, and digitalis (so used in toxicity) except colestyramine doesn't bind to them.

Therefore, other drugs except niacin should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid-binding resins.

2-These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥ 400 mg/dL).



V. Cholesterol absorption inhibitors



Example: Ezetimibe

- Decrease Intestinal absorption of dietary and biliary cholesterol.
- Effective even in absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile
- **No interactions**
- It lowers LDL cholesterol by approximately 17%.
- Due its modest LDL-lowering effects, ***ezetimibe* is often used as an adjunct to statin therapy or in**



VI- Omega-3 fatty acids



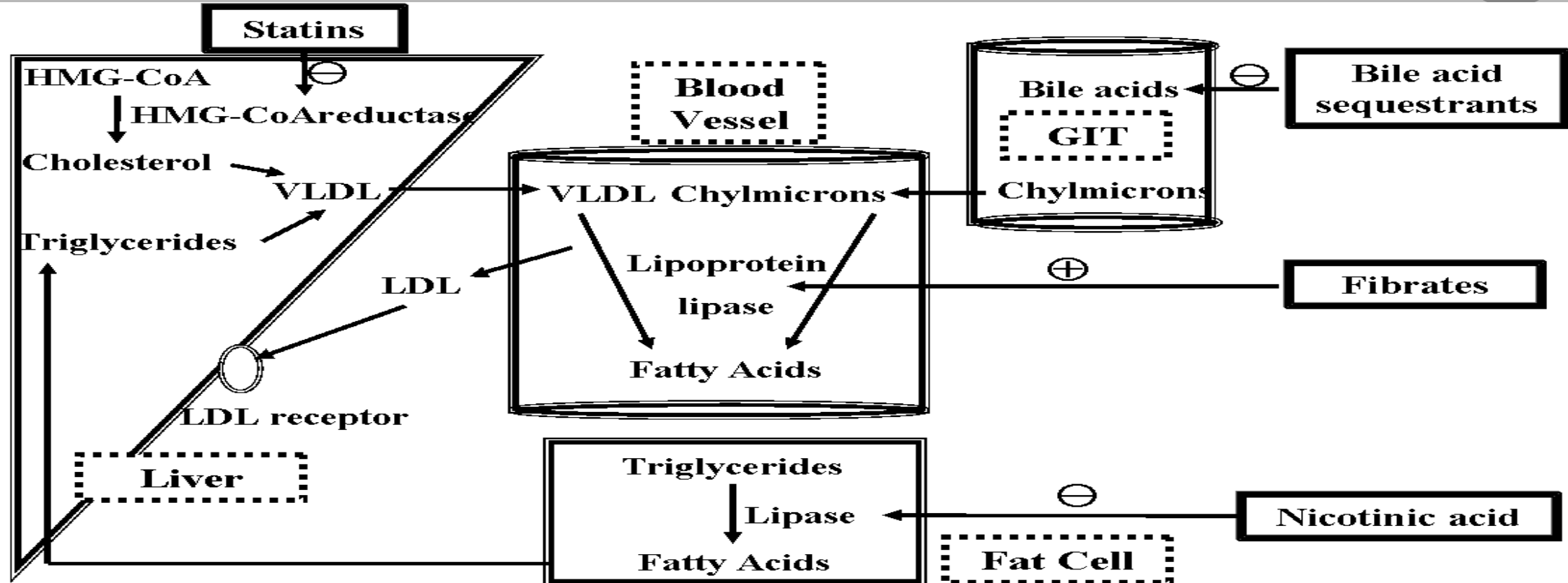
1. Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for **triglyceride lowering**.
2. Essential fatty acids **inhibit VLDL and triglyceride synthesis in the liver**.
3. They are found in **marine sources** such as tuna, halibut, and salmon.
4. Omega-3 PUFAs can be **considered as an adjunct to other lipid-lowering therapies** for individuals with significantly elevated triglycerides (≥ 500 mg/dL).
5. Although effective for triglyceride lowering, omega-3 PUFA supplementation **has not** been shown to reduce cardiovascular morbidity and mortality.
6. The most common side effects of omega-3 PUFAs **include**

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1. **GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste**

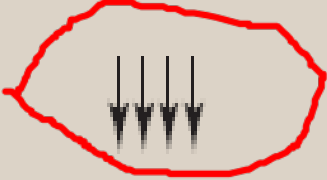
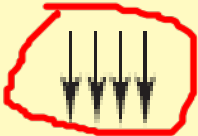
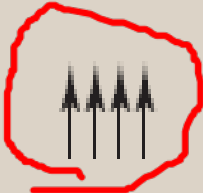
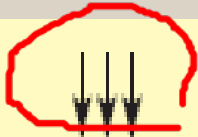


MANAGEMENT OF HYPERLIPIDEMIAS



<https://lh3.googleusercontent.com/HZd7ySQKwQ9wIBjVtLSkb82WwOc8rbHWffmkla8h9N4pYQVYWmjL-z07xlU8g3oBITVg=s152>



TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)			
Fibrates			
Niacin			
Bile acid sequestrants			
Cholesterol absorption inhibitor			

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Anti-hyperlipedemic combinations:



If no improvement within **6 weeks** with a single drug, dose should be . If no improvement after **3 months**, change the drug or consider combination therapy

Indications:

- 1. Increased VLDL during treatment of hypercholesterolemia with resins.**
- 2. Combined increase in LDL & VLDL.**
- 3. High LDL or VLDL not normalized with a single drug.**
- 4. Severe hypertriglyceridemia or**



Good combinations

1- Resin & Statin: (synergistic combination)

Adding statins block the compensatory increase that occurs in the rate of biosynthesis of cholesterol induced by resins.

very useful in lowering LDL-C levels.

2- Statin & Ezetimibe: (synergistic combination in hypercholesterolemia)

Statin blocks synthesis of endogenous cholesterol while ezetimibe blocks exogenous cholesterol.

3- Niacin & Statins:

In severe LDL elevation and combined hyperlipidemia



4- Niacin & Bile Acid-Binding Resins

- This combination effectively controls VLDL levels in disorders involving both increased VLDL and LDL levels.
- The drugs may be taken together, because niacin does not bind to the resins.

Bad combinations

4- Resin & fibrates:

Increase risk of cholelithiasis

5- Statins & Fibrates:

The combination of fenofibrate with rosuvastatin or pitavastatin is particularly effective.

Some other statins may interact unfavorably owing to effects on cytochrome P450 metabolism. Contraindicated (in full dose) because the incidence of myopathy and liver toxicity may



Combination of resins, ezetimibe, niacin, & reductase inhibitors

- These agents act in a complementary fashion to normalize cholesterol in patients with severe disorders involving elevated LDL.
- The effects are sustained, and little compound toxicity has been observed.
- Effective doses of the individual drugs may be lower than when each is used alone

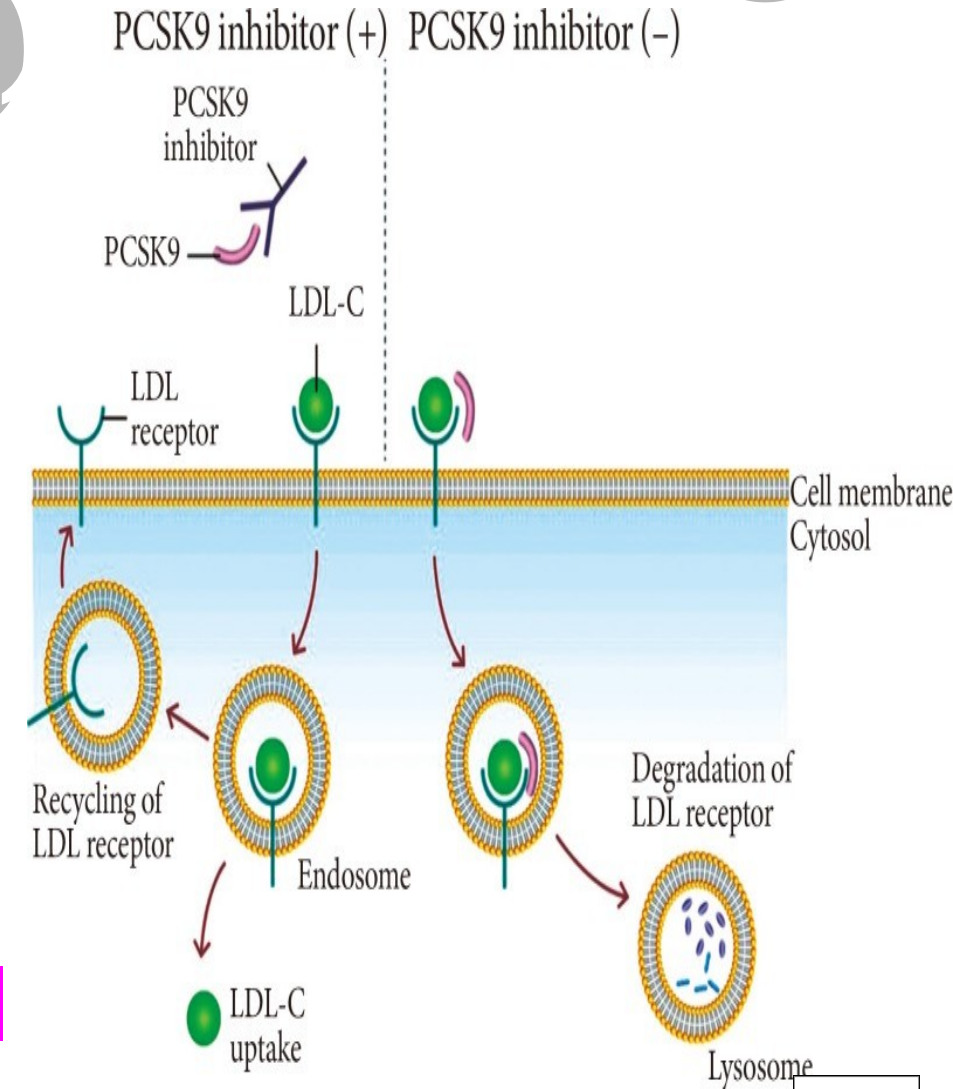


New Antihyperlipidemic drugs

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- PCSK9 is a protein encoded by the PCSK9 gene involved in the regulation of LDL-receptors on the surface of hepatocytes.
- Binding of PCSK9 to the low-density lipoprotein (LDL) receptor leads to the degradation of LDL receptor at lysosome.
- PCSK9 inhibitor, a monoclonal antibody against PCSK9, inhibits the binding of PCSK9 and LDL receptor, which results in the recycling of LDL receptor and increased expression of LDL receptor at cell membrane. LDL-C, low density lipoprotein cholesterol.

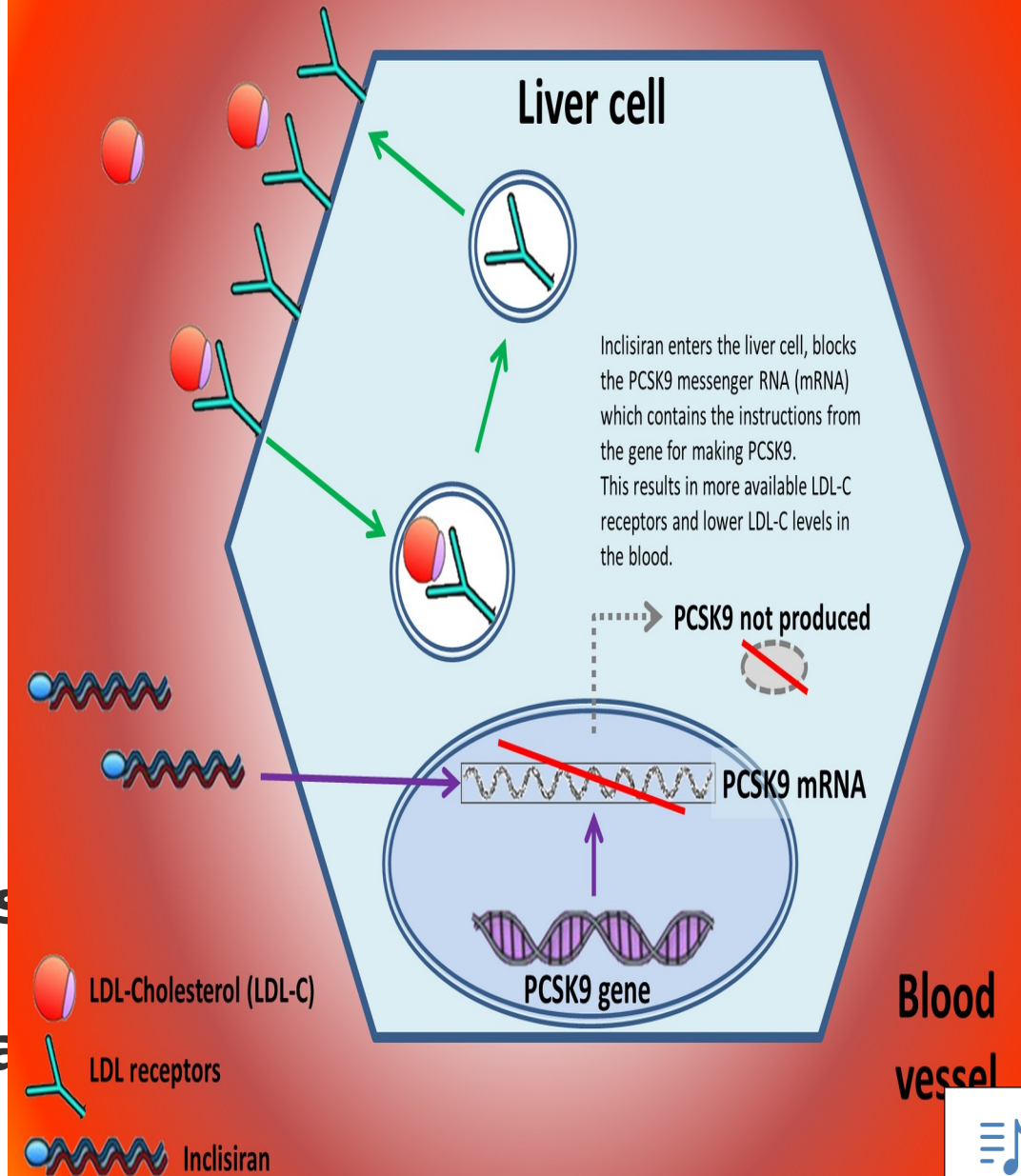


Inclisiran

- Inclisiran is a synthetic small interfering ribonucleic acid (RNA) that leads to the degradation of PCSK9-specific messenger RNA (mRNA) in the liver.
- The absence of PCSK9 results in the upregulation of LDL receptors and, consequently, lowers the circulating level of LDL cholesterol.
- It is a long-acting agent (1 to 2 times a year) that decreases PCSK9 production by the liver. It results in a reduction of LDL levels of >50%.

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2. What happens in the liver when inclisiran is present



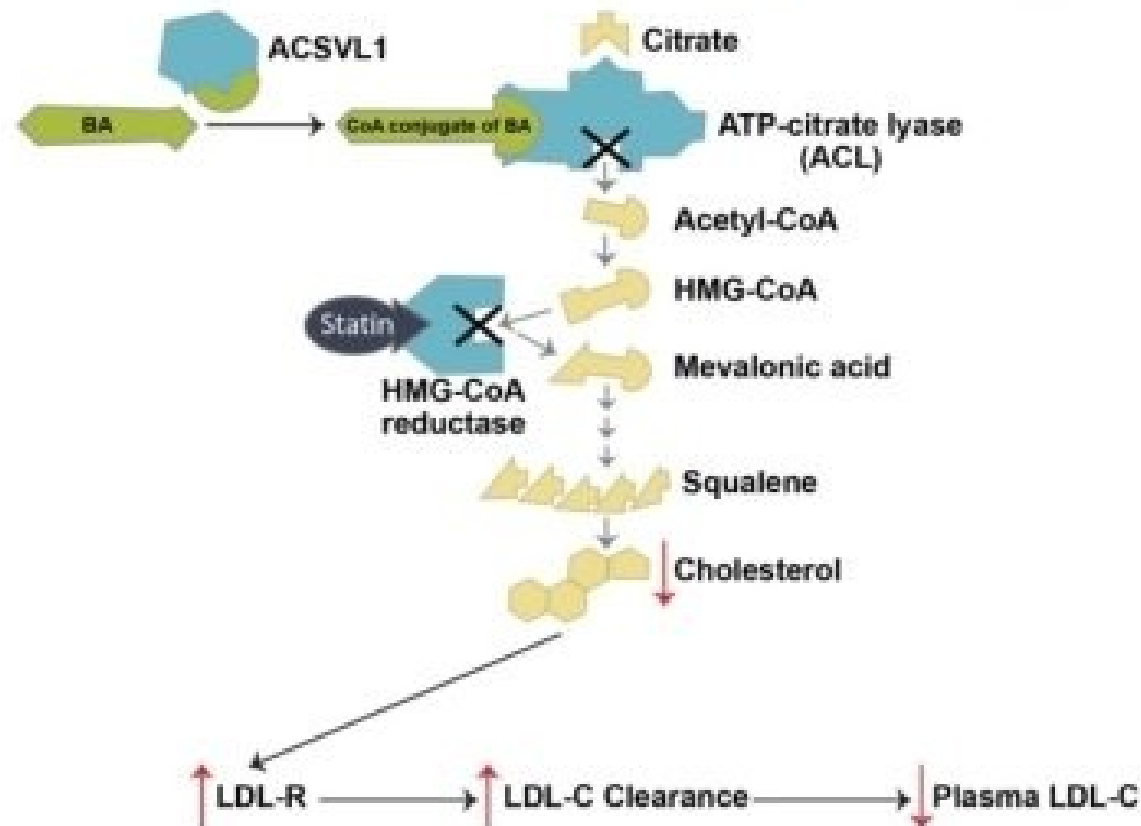
Bempedoic acid (BA)

- Bempedoic acid decreases LDL level through competitive inhibition of adenosine triphosphate citrate lyase (ACL), an enzyme responsible for catalysing the production of acetyl coenzyme A, an integral substrate in the cholesterol synthesis pathway in the liver.
- It acts in a similar way to statins, **upregulating the expression of the hepatic LDL receptor**, increasing the clearance of circulating LDL .
- It requires activation by an enzyme present in the liver, not in the muscles, decreasing the risks of muscle-related adverse effects, but there is an increase in uric acid and gout can occur.

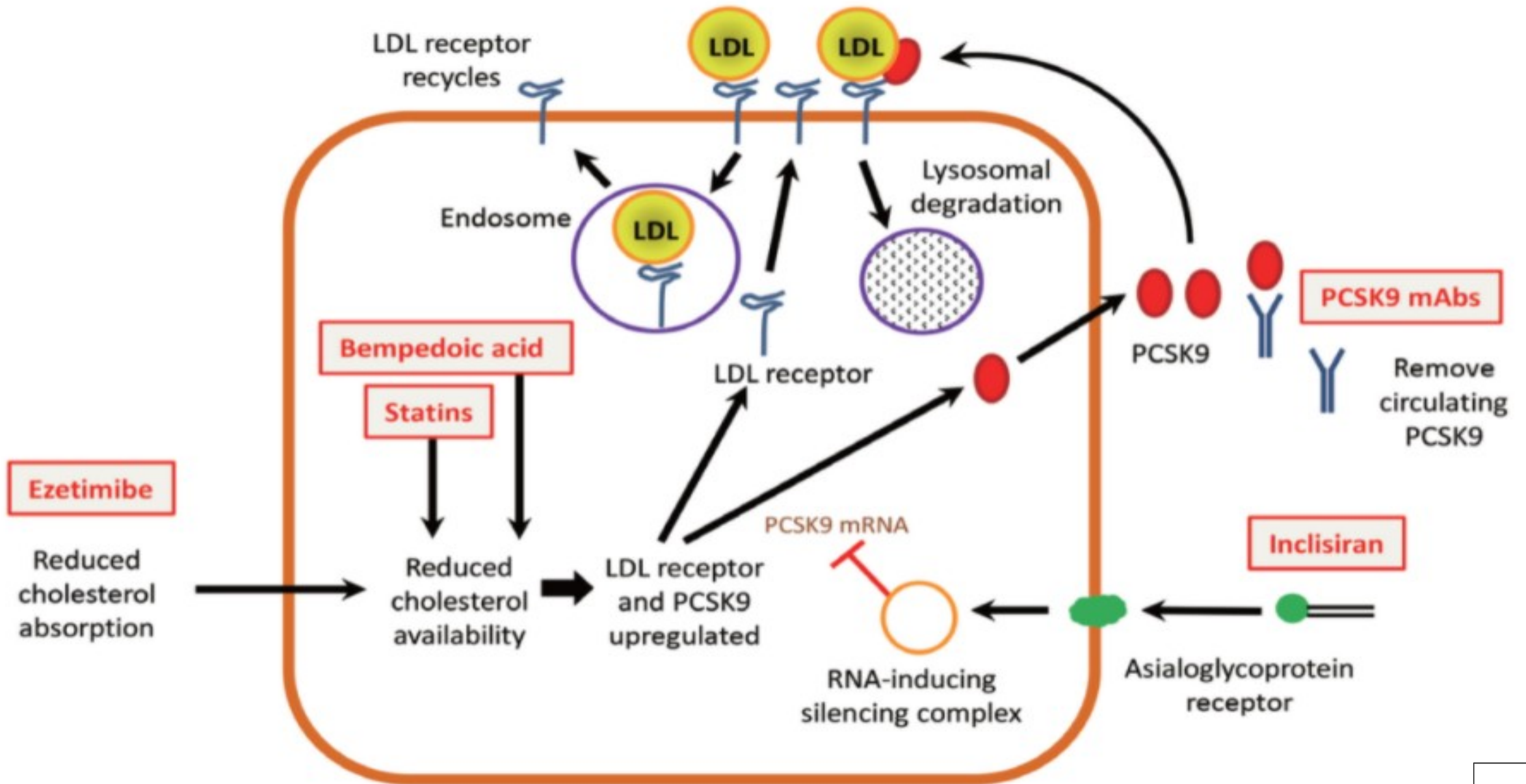


Bempedoic Acid Mechanism of Action

Converted to the CoA Conjugate of Bempedoic Acid, the Active Form, Only in Liver



- Bempedoic acid (BA) acts in the same cholesterol biosynthesis pathway as statins
- BA targets ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Upregulates LDL receptors and lowers LDL-C
- Specific isozyme (ACSVL1) that converts BA into an active drug is not present in skeletal muscle





1-Do you think that **Atenolol** is the best drug for his condition.

No

2- If not, what is the **best drug** for his condition?

Nitrates or Ca channel blocker

3-Do you need to **add** any drugs?

Hypolipidemic drugs



4-What is the **best drug that could be prescribed to him to decrease cholesterol? Mention its **mechanism of action**.**

Statins act by competitively inhibiting HMG-CoA reductase

5- What are the main **laboratory investigations that must be done before its prescription.**

serum transaminases, serum creatine kinase



If the patient doesn't show any improvement of the cholesterol level after 3 months.

1- Which drugs would you like to **combine** with it?

1- Resin & Statin: (**synergistic combination**)

2- Do you think combination with Statin & Ezetimibe (**synergistic combination**) is a favorable combination ?

Justify your answer.

Contraindicated (in full dose) because the incidence of myopathy and liver toxicity may increase so, use not more than $\frac{1}{4}$ maximum dose of statin



If the patient has hypertriglyceridemia reaching 300mg/dl while cholesterol was only 220 mg/dl.

1-Which **drug would you like to start with?**

2-What is its mechanism of action?

3-What is the main side effect?

1- fibrates

2-are agonists for peroxisome proliferator-activated receptor α (PPAR alpha) in muscle, liver, and other tissues.

3 a-GIT upset (most common).

b. Cholesterol gall stone formation (since fibrates increase the cholesterol content of bile),

Review questions



Which one of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3- methylglutaryl coenzyme A reductase?

- A. Fenofibrate.
- B. Niacin.
- C. Cholestyramine.
- D. Lovastatin.
- E. Gemfibrozil.

Review questions



JS is a 65-year-old man who presents to his physician for management of hyperlipidemia. His most recent lipid panel reveals an LDL cholesterol level of 165 mg/dL. His physician wishes to begin treatment to lower his LDL cholesterol levels. Which of the following therapies is the best option to lower JS's LDL cholesterol levels?

- A. Fenofibrate.
- B. Colesevelam.
- C. Niacin.
- D. Simvastatin.

Review questions



Which of the following patient populations is more likely to experience myalgia (muscle pain) or myopathy with use of HMG CoA reductase inhibitors?

- A. Patients with diabetes mellitus.
- B. Patients with renal insufficiency.
- C. Patients with gout.
- D. Patients with hypertriglyceridemia.
- E. Patients taking warfarin (blood thinner).



THANK YOU

SUGGESTED TEXTBOOKS



1- Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2- Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.